Qualitative control strategies for synchronization of bistable gene regulatory networks

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***Abstract*— In this paper we investigate the emergent dynamics in a network of N coupled cells, each expressing a similar genetic bistable switch. The bistable switch is modeled as a piecewise affine system and the cells are diffusively coupled. We show that both the coupling topology and the strength of the diffusion parameter may introduce new steady state patterns in the network. We study the synchronization properties of the coupled network and, using a control set of only three possible values (u_{min}, u_{max}, or 1), propose different control strategies which stabilize the system into a chosen synchronization pattern, both in the weak and strong coupling regimes. The results are illustrated by several numerical examples.**

I. INTRODUCTION

Piecewise-affine systems are now a frequently used framework for modeling genetic regulatory networks (see, for instance, [11], [15]). This type of systems has been used to model several distinct dynamical behaviors, such as, multistability (see, for instance, [5], [6], [19], [28]) or oscillatory behaviors (see, for instance, [5], [13], [14], [16], [20]). Diffusive coupling of identical sub-systems, where each pair of sub-systems are coupled by diffusion, and related synchronisation issues have attracted a large interest for years (see [2], [21], [25], [29], [32]). In [7], the authors have introduced coupling of piecewise affine systems by diffusion and have studied synchronization issues. The systems of genetic regulatory networks are coupled by discrete diffusion, that is, the dynamics is the sum of a reaction term corresponding to the individual bistable dynamics and a diffusion term described by symmetric Laplacian matrices, which define a coupling topology, so that the dynamics of the network can be seen as a space discretization of a system of two coupled reaction-diffusion pde's (see, for instance [4], [27] for results about the control of reaction-diffusion equations, [3] for synchronisation issues in reaction-diffusion pde's). If the individual system is a feedback loop in the sense developed, for instance in [11], [15], then the coupled system remains a piecewise affine system, but the dynamics is more complex than that of a higher dimensional feedback loop. Very often, networks can be partitioned into clusters, that is, subsets of nodes in which every subsystem has the same role in the network [21]. It is known that general diffusively coupled dynamical systems may give rise to different phenomenons. In particular, stability properties of the individual system may be modified and may depend on the strength of coupling, and cluster states can occur. In a general framework, the study of cluster state stability is a challenging issue [25], [32], both for oscillating and multistable individual systems.

Cells communicate by signaling to each other through cytokines such as growth factors [10]. Cell-to-cell communication may lead to emergent dynamical behaviour in a tissue or organ, such as tissue homeostasis [1], pattern formation [19], existence of multiple oscillatory regimes [17], etc. To study the new emergent dynamics in a network of similar genetic regulatory networks, we will consider N cells expressing a bistable switch and coupled through diffusion. The bistable switch is modeled as a piecewise affine system, a hybrid framework combining a linear system description in each region of the state space with discontinuous jumps in the vector fields between regions. The dynamics of the system within each state space region is easy to analyze and solutions are continuous, but the overall dynamics is still nonlinear due to the discontinuity of the vector fields. We are going to see that coupled piecewise affine systems may exhibit new steady states due to the coupling, corresponding to cluster states for the coupled system, which may turn out to be locally stable (see [7]). Through the coupling, a system with a given number of steady states is transformed into a much more complex one, which depends on the coupling graph topology and the coupling strength. Moreover, the location of these new steady states and their stability can be computed easily by a matrix inversion, so that cluster synchronization properties and patterns can be computed without resorting to abstract group theory [21]. Qualitatively speaking, consider an individual system with two steady states, and N-identical coupled systems. When the coupling strength is equal to zero, then the extended system has 2^N steady states corresponding to each subsystem converging to one of the two steady states of the individual dynamics, and the system has a boolean behaviour. When increasing the coupling strength, these steady state may undergo bifurcations depending on the graph topology, and may give rise to cluster states for the dynamics, at least in the weak coupling strength. For a strong coupling strength, we expect the system to converge to one of the full synchronized steady states, corresponding to the states where the subsystems are all synchronized at one of the two steady states of the individual system (see, for instance [26] for similar results concerning non-linear systems).

In order to avoid some "undesirable" biological states, or to reach a given synchronization pattern, one could be interested in controlling the system acting on gene expressions by modifying the production rates of some proteins belonging to a given set of cells. Such technique has been achieved

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experimentally for instance in synthetic biology [23], [24]. There exist different ways of acting on a group of cells and drive them to a synchronized state. For instance, the drug dexamethasone is known to synchronize cell clocks [17]. Other drugs can synchronize cells at a given phase of the cell cycle [8]. These drugs often act by activating or inhibiting the synthesis of some element, so we model this effect by a multiplicative control input on the production rate of one of the variables. This control value is qualitative in the sense that only three values ar allowed, u_{min}, u_{max}, or 1 (the latter corresponding to the uncontrolled case). This qualitative control comes from experimental limitations due to the poor quality of the measurements of gene expressions, and to the experimental limitations in the control itself.

The aim of this work is to understand the dynamics of such a system in the weak and strong coupling regime, and to propose control strategies which synchronize the subsystems belonging to the same cluster state.

Controlling coupled dynamical systems for synchronization is a challenging task, the feedback control problem for such purpose has been studied in the case of linear systems in [30]. However, to the best of the authors knowledge, very few results have been developed concerning the control of coupled piecewise affine systems, and especially control for their cluster synchronization. Here we propose to study a network of two dimensional bistable systems, and consider the problem of stabilizing its cluster states. In order to take biological constraints into account, we consider qualitative measurements, and propose to use a control which depends only on qualitative knowledge of the state variable, as in [6]. In this paper, we propose a control method which works for every type of coupling topology, and which is robust w.r.t. variations of the coupling strength.

In Section II, we present the individual dynamics. In Section III, we introduce the coupled dynamics and some of its basic properties. In Section IV, we focus on synchronization properties through the study of the steady states of the system in the weak coupling case. Then we propose control strategies ensuring synchronization of the cluster states of the system. In Section V, we study the dynamics in the strong coupling regime and propose a stabilization strategy ensuring full synchronization of the system at one of its two steady states.

II. Bistable switch individual system

Now we recall a classical model describing a bistable switch that has been implemented experimentally in [18], and studied mathematically for instance in [6]. Consider two variables x_1 and x_2 which represent two proteins mutually inhibiting each other. The individual dynamics, defined in Filippov sense, is the following

$$\begin{aligned} \dot{x}_1 &= -\gamma_1 x_1 + k_1 s^-(x_2,\theta_2) \\ \dot{x}_2 &= -\gamma_2 x_2 + k_2 s^-(x_1,\theta_1), \end{aligned} \tag{1}$$

where for $j \in \{1,2\}$, $x_j \in \mathbb{R}$, and for $\theta \in \mathbb{R}$, $s^-(\cdot,\theta) : \mathbb{R} \to \mathbb{R}$ is such that $s^-(x,\theta) = 0$ if $x > \theta$, and $s^-(x,\theta) = 1$ if $x < \theta$. It is assumed that $s^-(x) \in [0,1]$ for $x = \theta$. The positive constants $(\gamma_j)_{j\in\{1,2\}}$, $(k_j)_{j\in\{1,2\}}$ correspond, respectively, to the degradation and the production rates of each variable. It is a classical fact (see [6]) that the domain $K = [0, \frac{k_1}{\gamma_1}] \times [0, \frac{k_2}{\gamma_2}]$ is forward invariant by the dynamics of Equation (1). From now on we consider only solutions evolving in K.

Define the regular domains

$$\begin{aligned} B_{00} &= \{x = (x_1,x_2) \in \mathbb{R}^2 \mid 0 < x_1 < \theta_1,\ 0 < x_2 < \theta_2\}, \\ B_{01} &= \{x = (x_1,x_2) \in \mathbb{R}^2 \mid 0 < x_1 < \theta_1,\ \theta_2 < x_2 < \tfrac{k_2}{\gamma_2}\}, \\ B_{10} &= \{x = (x_1,x_2) \in \mathbb{R}^2 \mid \theta_1 < x_1 < \tfrac{k_1}{\gamma_1},\ 0 < x_2 < \theta_2\}, \\ B_{11} &= \{x = (x_1,x_2) \in \mathbb{R}^2 \mid \theta_1 < x_1 < \tfrac{k_1}{\gamma_1},\ \theta_2 < x_2 < \tfrac{k_2}{\gamma_2}\}. \end{aligned}$$

For a piecewise affine system defined on $\mathbb{R}^n$ whose dynamics restricted to a regular domain B is a linear dynamical system having an asymptotically stable equilibrium, define the focal point on B as this equilibrium point. Notice that this point may belong to B or not. Each region B_{ij} has a focal point, $\phi_{ij} = (\bar{x}_i, \bar{x}_j)$ corresponding to $\bar{x}_i = \frac{k_i}{\gamma_i} s^-(\bar{x}_j, \theta_j)$. Equation (1) has two locally asymptotically stable steady states, $\phi_{10} = (\frac{k_1}{\gamma_1}, 0) \in B_{10}$ and $\phi_{01} = (0, \frac{k_2}{\gamma_2}) \in B_{01}$, and an unstable Filippov equilibrium point at (θ_1, θ_2). In addition, there exists a curve, called separatrix (see Appendix VI-A.1 with $u \equiv 1$), passing through (θ_1, θ_2) and dividing K in two regions (above and below) such that the solutions of Equation (1) defined in Filippov sense reach B_{01} or B_{10}, respectively, in finite time. Moreover, B_{10} (respectively, B_{10}) is included in the bassin of attraction of ϕ_{10} (respectively, ϕ_{01}). In Section IV-B, we will assume that Assumption (H) is satisfied, while in the other sections, the only required assumption is $\theta_j < \frac{k_j}{\gamma_j},\ j \in \{1,2\}$.

III. Coupled system

In this paper we study a network of $N \in \mathbb{N}$ identical systems whose individual dynamics is given by Equation (1), which are coupled by diffusion, as it has been studied in a slightly different setting in [7]. As shown below, due to the diffusion term, the steady states corresponding to ϕ_{10} or ϕ_{01} will be shifted. In particular, the steady states of such a system correspond to the limit trajectories of systems such that every subsystem has initial conditions in B_{01} or B_{10}, and they depend on the initial location of the subsystems. One could expect that the more numerous initial conditions are in B_{01} (respectively, B_{10}), the closer the steady state is to Φ_{01} (respectively, Φ_{10}), where Φ_{01} (respectively, Φ_{10}) is the state of the coupled system where every subsystem is in the state ϕ_{10} (respectively, ϕ_{10}). In our study, we are going to see that the location of the steady states depend on more complicated coupling graph properties, so that the previous assertion is not true in general, and we will show that the steady states are narrowly linked to synchronization properties of the cluster states of the network, that is, subsets of nodes in which every subsystem has the same role in the network.

We observe different dynamical behaviours, which depend on the value of the coupling terms. For small enough coupling terms, cluster states can be stable (see Section IV), while when there are all larger than a given value (see Section V), the only stable steady states are Φ_{01} and Φ_{10}, that is, the *synchronized steady states*, where every node of the network has the same state.

A. Dynamics of the coupled system

Let $N \in \mathbb{N}$. Define, for $j \in \{1,2\}$, $x_j = (x_{j,k})_{k\in\{1,\dots,N\}} \in \mathbb{R}^N$, and the N-dimensional vector

$$q(x_j,\theta) = \begin{pmatrix} s^-(x_{j,1},\theta) \\ \vdots \\ s^-(x_{j,N},\theta) \end{pmatrix}.$$

Define for every $x = (x_{j,k})_{(j,k)\in\{1,2\}\times\{1,\dots,N\}} \in \mathbb{R}^{2N}$ the canonical projection $\pi_j(x) = x_j$ for $k \in \{1,2\}$.

Consider the following equation

$$\begin{aligned} \dot{x}_1 &= -(\Gamma_1 + L_1)x_1 + k_1 q(x_2,\theta_2) \\ \dot{x}_2 &= -(\Gamma_2 + L_2)x_2 + k_2 q(x_1,\theta_1), \end{aligned} \tag{2}$$

whose solutions can be defined in the Fillipov sense, where, $(\gamma_j)_{j\in\{1,2\}}$, $(k_j)_{j\in\{1,2\}}$ satisfy Assumption (H) given in Appendix VI-A, and $\Gamma_j = \gamma_j \mathrm{Id}_{\mathbb{R}^N}$. For every $k \in \{1,\dots,N\}$, the pair $(x_{1,k},x_{2,k})$ is called the *k-th subsystem* of Equation (2), and for $j \in \{1,2\}$, $x_{j,k}$ is called the *x_j-coordinate* of the k-th subsystem. We present here a list of important assumptions and properties for Equation (2).

- **Graph Laplacian Matrices:** The matrix L_j is a Laplacian N-dimensional symmetric matrix, that is, its coefficients $(l^j_{kl})_{k,l\in\{1,\dots,N\}}$ satisfy
$$l^j_{kl} = \begin{cases} \sum_{i\neq k} a_{ki}, \ l = k \\ -a_{kl}, \ l \neq k, \end{cases}$$
where $a_{kl} \geq 0$ for every $k,l \in \{1,\dots,N\}$, and assume that for $j \in \{1,2\}$, L_j defines a strongly connected graph $\mathscr{G}_j$. Denote the set of such matrices by $\mathrm{Lap}_N(\mathbb{R})$. Very often, L_j is chosen such that $a_{kl} \neq 0$ with $k \neq l$ implies $a_{kl} = -1$, and we replace L_j by $\alpha_j L_j$ in Equation (2), where $\alpha_j > 0$ is called the *homogeneous coupling strength*.
- **Regular domains:** Define the regular domains of Equation (2) as the cartesian products of the domains $(B_{jk})_{j,k\in\{0,1\}}$ defined in Section II. More precisely, for a sequence $(j_l,k_l)_{l\in\{1,\dots,N\}}$ such that for every $l \in \{1,\dots,N\}$, $(j_l,k_l) \in \{0,1\}^2$, we say that $x \in B_{j_1,k_1} \times \dots \times B_{j_N,k_N}$ if for every $l \in \{1,\dots,N\}$, $(x_{1,l},x_{2,l}) \in B_{j_l,k_l}$. One can show that the full domain K^N, where K is defined in Section II, is forward invariant by the dynamics of Equation (2).
- **Focal points and steady states:** For a regular domain B of K^N the focal point corresponding to the domain B is given by
$$\begin{aligned} \bar{x}_1 &= k_1(\Gamma_1 + L_1)^{-1} q(\pi_2(B),\theta_2) \\ \bar{x}_2 &= k_2(\Gamma_2 + L_2)^{-1} q(\pi_1(B),\theta_1), \end{aligned} \tag{3}$$
where, by abuse of notations, $q(\pi_j(B))$ is the constant value taken by q in the set $\pi_j(B)$, for every $j \in \{1,2\}$. It follows easily that $(\bar{x}_1,\bar{x}_2)$ is a steady state when $(\bar{x}_1,\bar{x}_2) \in B$, that is
$$\begin{aligned} \bar{x}_1 &= k_1(\Gamma_1 + L_1)^{-1} q(\bar{x}_2,\theta_2) \\ \bar{x}_2 &= k_2(\Gamma_2 + L_2)^{-1} q(\bar{x}_1,\theta_1). \end{aligned} \tag{4}$$
Because of the Laplacian structure of $(L_j)_{j\in\{1,2\}}$, the matrix $-(\Gamma_j + L_j)$ is Hurwitz. Hence, the steady states are stable in the following sense: for every initial condition in B, the system converges to the steady state given by Equation (4). Define $x = \Phi_{10} \in \mathbb{R}^{2N}$ such that for every $k \in \{1,\dots,N\}$, $(x_{1,k},x_{2,k}) = \phi_{10}$. Define $\Phi_{01} \in \mathbb{R}^{2N}$ similarly. Φ_{10} and Φ_{01}, that we call *synchronized steady-states* of Equation (2) are independent from the coupling terms L_1 and L_2.

In this article, we focus on the following properties for solutions of Equation (2).

Definition 3.1:
- A subset $S \subset \{1,\dots,N\}$ achieves *synchronization* if for every $q,q' \in S$, $||(x_{1,q}(t),x_{2,q}(t)) - (x_{1,q'}(t),x_{2,q'}(t))|| \to 0$ when $t \to +\infty$.
- When the subsystems belonging to S converge to some constant steady state value, we say that they achieve *consensus*.

One may be interested in synchronizing different subset of $\{1,\dots,N\}$ simultaneously. The main question is the following:

- Given of partition of $\{1,\dots,N\}$, is it possible for subsystems belonging to the same element of the partition to converge towards the same state ?

For this, a natural notion is the so called *cluster synchronization*.

Definition 3.2:
- A partition $(S_j)_{j\in t\{1,\dots,k\}}$ of $\{1,\dots,N\}$ achieves *cluster synchronization* when for every $j \in \{1,\dots,k\}$ and $q,q' \in S_j$, $||(x_{1,q}(t),x_{2,q}(t)) - (x_{1,q'}(t),x_{2,q'}(t))|| \to 0$ when $t \to +\infty$.
- When for every $j \in \{1,\dots,k\}$ the subsystems belonging to S_j converge to some common constant steady state value, we say that they achieve *cluster consensus*.

B. Control of the dynamics

Assume that we have a control $u : \mathbb{R} \to \mathbb{R}^{2N}$ acting on the systems such that the k-th subsystem is controlled as:

$$\begin{aligned} \dot{x}_{1,k} &= -\gamma_1 x_{1,k} + u^1_k(t) k_1 s^-(x_{2,k},\theta_2) + \textstyle\sum_{j=1}^N l^1_{kj}(x_{1,j} - x_{1,k}) \\ \dot{x}_{2,k} &= -\gamma_2 x_{2,k} + u^2_k(t) k_2 s^-(x_{1,k},\theta_1) + \textstyle\sum_{j=1}^N l^2_{kj}(x_{2,j} - x_{2,k}), \end{aligned} \tag{5}$$

where, for $j \in \{1,2\}$, $L_j = (l^j_{kq})_{k,q\in\{1,\dots,N\}}$. We aim at finding u, whose components are $(u^1_k,u^2_k)_{k\in\{1,\dots,N\}}$, that stabilizes the steady states of Equation (2). The control $u \equiv u(t,x(t))$ is assumed to act on the production rates of each variable. It is assumed to depend only on $t \geq 0$ and on the regular domain to which the solution $x(t)$ of Equation (5) at time t belongs, and for $j \in \{1,2\}$, $k \in S$, u^j_k has values in a finite set of the form $\{u_{\min},1,u_{\max}\}$, where $u_{\max} \geq 1$ and $u_{\min} \geq 0$. Note that u changes the location of the focal points of Equation (2). The choice of u depends on our needs. Indeed, in Section IV-C, we choose different controls for the subsystems belonging to a subset S of subsystems than those that do not belong to S. In Section V, we will see that it may be sufficient to act on a strict subset of subsystems in order to control the whole system, because the variations of the control terms "propagate" into the network in the strong coupling regime.

IV. Synchronization in the weak coupling regime

In this section, we study the dynamics in the weak coupling regime, and we propose a control strategy ensuring stabilization of the steady states.

A. Steady states and synchronization properties of the uncontrolled system

Let $(e_j)_{j\in\{1,\ldots,N\}}$ be the canonical basis of $\mathbb{R}^N$. For every $S \subset \{1,\ldots,N\}$, define

$$X_S = \sum_{j\in S} e_j,$$

and the regular domain

$$B_S = \prod_{j\in\{1,\ldots,N\}} B_j,$$

where $B_j = B_{01}$ if $j \in S$, else $B_j = B_{10}$. We introduce the following weak coupling condition, which expresses the property that the focal point of the uncontrolled system corresponding to the regular domain B of K^N defined by Equation (3) is located in the same regular domain as the one obtained when $L_j = 0$ for $j \in \{1,2\}$.

Definition 4.1 (Weak coupling): Consider for $i \in \{1,2\}$, $L_i \in \mathrm{Lap}_N(\mathbb{R})$. We say that (L_1, L_2) satisfies the *weak diffusion condition* if for every $S \subset \{1,\ldots,N\}$, $j \in \{1,\ldots,N\}$ and $i \in \{1,2\}$,

$$\begin{aligned} \left((\Gamma_i + L_i)^{-1} X_S\right)_j &< \frac{\theta_i}{k_i} \quad \text{for } j \notin S \\ \left((\Gamma_i + L_i)^{-1} X_S\right)_j &> \frac{\theta_i}{k_i} \quad \text{for } j \in S. \end{aligned} \tag{W}$$

Remark 4.2: Concerning the solvability of the constraint (W), notice that the choice $L_i = 0$ satisfies (W). By a continuity argument, for every $L_1, L_2 \in \mathrm{Lap}_N(\mathbb{R})$, there exists $\alpha_1^0, \alpha_2^0 > 0$ such that $(\alpha_1 L_1, \alpha_2 L_2)$ satisfies the weak diffusion condition for every $(\alpha_1, \alpha_2) \in [0, \alpha_1^0] \times [0, \alpha_2^0]$.

Assume in this section that diffusion acts only on the x_1-coordinate, that is, $L_2 = 0$, and $L_1 = L$ is a $N \times N$ Laplacian matrix of a strongly connected graph $\mathscr{G}$. The set $\{1,\ldots,N\}$ constitutes the nodes of $\mathscr{G}$, and we denote the set of automorphisms of $\mathscr{G}$ by $\mathrm{Aut}(\mathscr{G})$.

Assume moreover that **Condition** (W) **holds.** Consider the following equation

$$\begin{aligned} \dot{x}_1 &= -(\Gamma_1 + L)x_1 + k_1 q(x_2, \theta_2) \\ \dot{x}_2 &= -\Gamma_2 x_2 + k_2 q(x_1, \theta_1), \end{aligned} \tag{6}$$

where $\Gamma_j = \gamma_j \mathrm{Id}_{\mathbb{R}^N}$, with $\gamma_j > 0$. Then Equation (4) of steady states can be simplified into

$$\begin{aligned} \bar{x}_1 &= k_1 (\Gamma_1 + L)^{-1} q(\bar{x}_2, \theta_2) \\ \bar{x}_2 &= k_2 \Gamma_2^{-1} q(\bar{x}_1, \theta_1). \end{aligned} \tag{7}$$

One can prove that every solution of Equation (7) belongs to a regular domain B_S where $S \subset \{1,\ldots,N\}$, and to every regular domain B_S corresponds a unique steady state solution of Equation (7), which belongs to B_S. In other words, in the weak coupling regime, every steady state given by Equation (7) has components in B_{01} or B_{10}. Moreover, the regular domain B_S is forward invariant by Equation (6).

We introduce the notions of *admissible* subsets of $\{1,\ldots,N\}$, *cluster admissible partitions* which are related to synchronization properties of Equation (6) (see Figure 1 for a graphical illustration of such properties). A remarkable feature of the studied system is that these properties can be checked by linear algebra methods, and does not require graph and group theoretical tools as it is needed most of the time when we aim at understanding synchronization properties of dynamical systems (see, for instance, [21], [25], [32]).

Definition 4.3: We say that $S \subset \{1,\ldots,N\}$ is *set-admissible* in $\{1,\ldots,N\}$ if the steady state of Equation (6) corresponding to the regular domain B_S has the same j-th component for every $j \in S$, that is, if $\langle (\Gamma_1 + L)^{-1} X_S, e_j \rangle = \langle (\Gamma_1 + L)^{-1} X_S, e_k \rangle$, for every $j, k \in S$.

Remark 4.4:
- For $S \subset \{1,\ldots,N\}$, define $\tilde{X}_S = \sum_{j\in\{1,\ldots,N\}} e_j - X_S$. Then S is set-admissible if and only if $\langle (\Gamma_1 + L)^{-1} \tilde{X}_S, e_j \rangle = \langle (\Gamma_1 + L)^{-1} \tilde{X}_S, e_k \rangle$, for every $j, k \in S$.
- Notice that $S = \{1,\ldots,N\}$ is set-admissible, independently of the choice of L. Indeed the identity $L X_{\{1,\ldots,N\}} = 0$ implies $(\Gamma_1 + L) X_{\{1,\ldots,N\}} = \gamma_1 X_{\{1,\ldots,N\}}$, and hence $(\Gamma_1 + L)^{-1} X_{\{1,\ldots,N\}} = \frac{1}{\gamma_1} X_{\{1,\ldots,N\}}$.

We introduce the following notion, which is stronger than the notion of set-admissibility defined in Definition 4.3, and is illustrated on Figure 1(b).

Definition 4.5:
- We say that a partition $(S_j)_{j\in\{1,\ldots,k\}}$ of $\{1,\ldots,N\}$ is *cluster admissible* if for every $X \in \{0,1\}^N$ such that for every $i \in \{1,\ldots,k\}$, $\langle X, e_j \rangle = \langle X, e_q \rangle$ for every $j, q \in S_i$, we have that, for every $i \in \{1,\ldots,k\}$, the quantity $\langle (\Gamma_1 + L)^{-1} X, e_q \rangle$ is independent of $q \in S_i$.
- For a cluster admissible partition $(S_j)_{j\in\{1,\ldots,k\}}$ of $\{1,\ldots,N\}$, for every j, S_j is called a *cluster*.

Proposition 4.6 (Consensus of an admissible subset): Let S be an admissible subset of $\{1,\ldots,N\}$, and assume that the solution $x(t)$ of Equation (6) satisfies $x(0) \in B_S$. Then there exists $\bar{x} \in B_{01}$ (respectively, B_{10}), corresponding to the components on S of the steady state obtained in the forward invariant regular domain B_S, such that for every $j \in S$, $(x_{1,j}(t), x_{2,j}(t)) \to \bar{x}$ when $t \to +\infty$.

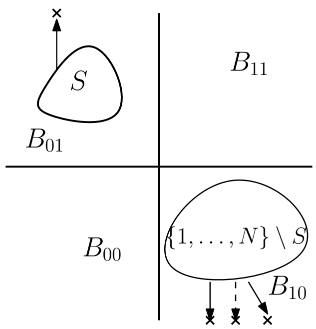
Proof: The matrix $-(\Gamma_1 + L)$ being Hurwitz, $x(t)$ converges to the steady state $\bar{x} = (\bar{x}_1, \bar{x}_2)$ such that $\bar{x}_1 = (\Gamma_1 + L)^{-1} q(x_2(0), \theta_2)$ and $\bar{x}_2 = (\Gamma_2)^{-1} q(x_1(0), \theta_1)$ when $t \to \infty$. Under the assumption of the proposition, we get that $\bar{x}_{1,k} = \langle (\Gamma_1 + L)^{-1} q(x_2(0), \theta_2), e_k \rangle$ does not depend on $k \in S$. The result follows. ■

By the same argument, we obtain the following result, which shows that each cluster of a cluster admissible partition achieves consensus, provided that the subsystems belonging to a given cluster belong to the same regular domain B_{01} or B_{10}.

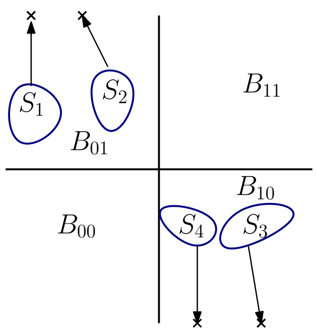
Proposition 4.7 (Cluster consensus): Let $(S_i)_{i\in\{1,\ldots,k\}}$ be a cluster admissible partition of $\{1,\ldots,N\}$. Assume that the solution $x(t)$ of Equation (6) satisfies, for every $i \in \{1,\ldots,k\}$,

$\forall j \in S_i$, $(x_{1,j}(0), x_{2,j}(0)) \in B_{\eta_i}$, where $\eta_i = 10$ or 01. Then for every $i \in \{1,\dots,k\}$, there exists $\bar{x}_i \in B_{\eta_i}$ such that for every $j \in S_i$, $(x_{1,j}(t), x_{2,j}(t)) \to \bar{x}_i$ when $t \to +\infty$.

Remark 4.8: The $(\bar{x}_i)_{i\in\{1,\dots,k\}}$ are the components of the steady state of Equation (6) belonging to the regular domain $\prod_{j\in\{1,\dots,N\}} B_{\eta_j}$, where, by a slight abuse of notations, $\eta_j = \eta_i$ if $j \in S_i$.



(a) Set-admissibility: subsystems belonging to S converge to the same state in the weak coupling regime.



(b) Cluster admissible partition: subsystems in the same subset S_j for $j \in \{1,\dots,4\}$ converge to the same state in the weak coupling regime.

Fig. 1. Illustration of the notions of set-admissibility and cluster admissible partitions

Even if, in our case, admissibility of a set $S \subset \{1,\dots,N\}$ and cluster admissible partitions can be computed by linear algebra methods, we see easily that some group symmetry properties of the coupling graph $\mathscr{G}$ imply these properties, as we will see in the lemmas 4.10 and 4.11. However, as already noticed in [32], there exists cluster states and hence set-admissible subsets which are not due to symmetries of the coupling graph $\mathscr{G}$, such as, in general, the set $S = \{1,\dots,N\}$, which corresponds to a synchronized steady state. We present the following basic result, which is an adaptation of very classical results (see, for instance [21, Section III]) to our particular setting.

Lemma 4.9: Let $\sigma \in \mathrm{Aut}(\mathscr{G})$ and $X \in \{0,1\}^N$ such that $\langle X, e_i\rangle = \langle X, e_{\sigma(i)}\rangle$ for every $i \in \{1,\dots,N\}$. Then for every $i \in \{1,\dots,N\}$, $\langle (\Gamma_1 + L)^{-1} X, e_i\rangle = \langle (\Gamma_1 + L)^{-1} X, e_{\sigma(i)}\rangle$.

Proof: Let $\sigma \in \mathrm{Aut}(\mathscr{G})$ and let P be the $n \times n$ permutation matrix associated with σ. By definition of σ, P commutes with L, and hence with $(\Gamma_1 + L)^{-1}$. The result follows. ■

The next two lemmas are direct consequences of Lemma 4.9.

Lemma 4.10: If S is an orbit of an element of $\{1,\dots,N\}$ under the action of a subgroup $\mathscr{H}$ of $\mathrm{Aut}(\mathscr{G})$ on $\{1,\dots,N\}$, then S is set-admissible.

We present the following result, which is an extension of Lemma 4.10, whose proof follows from Lemma 4.9.

Lemma 4.11: Let $(S_j)_{j\in\{1,\dots,k\}}$ be the orbits of the action of a subgroup $\mathscr{H}$ of $\mathrm{Aut}(\mathscr{G})$ on $\{1,\dots,N\}$. Then $(S_j)_{j\in\{1,\dots,k\}}$ is a cluster admissible partition of $\{1,\dots,N\}$.

In the each of the following examples, **we consider a Laplacian Matrix $\tilde{L}$ and $L = \alpha\tilde{L}$**, where $\alpha > 0$ is the homogeneous coupling strength is such that L satisfies Condition (W), and we denote the solution of Equation (16) with initial condition $x(0)$ by $x(t)$ for $t \geq 0$.

We first give an example of coupling topology such that every subset of $\{1,\dots,N\}$ is set-admissible, as illustrated on Figure 2, where we show that the subsystems in B_{01} (respectively, B_{10}) converge to a common state $\bar{x}$ (respectively, $\tilde{x}$), that is, the system achieves consensus both in B_{01} and B_{10}.

Example 4.12 (All to all interconnection): Let $\tilde{L}$ be the $N \times N$ Laplacian matrix defined by

$$\tilde{L} = \begin{pmatrix} N-1 & -1 & \cdots & \cdots & \cdots & -1 \\ -1 & N-1 & \ddots & \ddots & \ddots & \vdots \\ \vdots & \ddots & N-1 & \ddots & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & N-1 & -1 \\ -1 & \cdots & \cdots & \cdots & -1 & N-1 \end{pmatrix}.$$

Define, for $i, j \in \{1,\dots,N\}$, $a_{ij} = \langle (\Gamma_1 + L)^{-1} e_i, e_j\rangle$. By similar computations as in [7, Section 4.1], every subset of $\{1,\dots,N\}$ is set-admissible. Let $S \subset \{1,\dots,N\}$ whose cardinality is equal to k. Assume that $\forall j \in S$, $(x_{1,j}(0), x_{2,j}(0)) \in B_{01}$ and $\forall j \notin S$, $(x_{1,j}(0), x_{2,j}(0)) \in B_{01}$. Then there exists $\bar{x} \in B_{01}$ and $\tilde{x} \in B_{10}$, depending only on α, k and N such that the solution $x(t)$ of Equation (6) satisfies for every $j \in S$, $(x_{1,j}(t), x_{2,j}(t)) \to \bar{x}$ and for every $j \notin S$, $(x_{1,j}(t), x_{2,j}(t)) \to \tilde{x}$, when $t \to +\infty$. Moreover, the more numerous the subsystems in B_{01} (respectively, B_{10}) are, the nearest $\bar{x}$ (respectively, $\tilde{x}$) is to ϕ_{01} (respectively, ϕ_{10}).

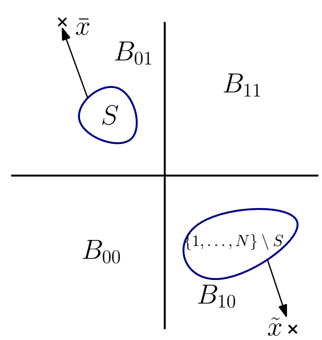


Fig. 2. Synchronizability in the case of all to all interconnection coupling topology, as in Example 4.12.

One could expect that the more numerous subsystems are in the same regular domain, the easier they synchronize.

However, this is not the case, as shown in this example, where synchronization between the two subsystems 1 and 2 is lost by adding subsystem 3 to the regular domain B_{01}.

Example 4.13 (Loss of synchronization): Let $\tilde{L}$ be the 4×4 Laplacian matrix defined by

$$\tilde{L} = \begin{pmatrix} 2 & -1 & 0 & -1 \\ -1 & 2 & -1 & 0 \\ 0 & -1 & 2 & -1 \\ -1 & 0 & -1 & 2 \end{pmatrix}.$$

We have that the matrix $\gamma_1(\gamma_1+4\alpha)(\Gamma_1+\alpha\tilde{L})^{-1}$ is equal to

$$\begin{pmatrix} \frac{\gamma_1^2+4\gamma_1\alpha+2\alpha^2}{\gamma_1+2\alpha} & \alpha & \frac{2\alpha^2}{\gamma_1+2\alpha} & \alpha \\ \alpha & \frac{\gamma_1^2+4\gamma_1\alpha+2\alpha^2}{\gamma_1+2\alpha} & \alpha & \frac{2\alpha^2}{\gamma_1+2\alpha} \\ \frac{2\alpha^2}{\gamma_1+2\alpha} & \alpha & \frac{\gamma_1^2+4\gamma_1\alpha+2\alpha^2}{\gamma_1+2\alpha} & \alpha \\ \alpha & \frac{2\alpha^2}{\gamma_1+2\alpha} & \alpha & \frac{\gamma_1^2+4\gamma_1\alpha+2\alpha^2}{\gamma_1+2\alpha} \end{pmatrix}.$$

Define, for $i,j\in\{1,\dots,4\}$, $a_{ij} = \langle(\Gamma_1+L)^{-1}e_i,e_j\rangle$. The set $\{1,2\}$ is set-admissible because of the identity $a_{11}=a_{22}$, hence subsystems 1 and 2 achieve consensus for Equation (6), when subsystems 1 and 2 are initially in B_{01} while subsystems 3 and 4 are initially in B_{10}. However, $\langle(\Gamma_1+L)^{-1}(e_1+e_2+e_3),e_1\rangle \neq \langle(\Gamma_1+L)^{-1}(e_1+e_2+e_3),e_2\rangle$, hence subsystems 1 and 2 do not achieve consensus when subsystems 1, 2 and 3 are initially in B_{01} while subsystem 4 is initially in B_{10}. In particular, the set $\{1,2,3\}$ is not set-admissible.

In the next two examples, we give important properties of some very classical coupling topologies, which will be illustrated numerically in Section IV-C.

Example 4.14 (Chain graph): Let $\tilde{L}$ be the $N\times N$ Laplacian matrix defined by

$$\tilde{L} = \begin{pmatrix} 1 & -1 & 0 & \cdots & \cdots & 0 \\ -1 & 2 & \ddots & \ddots & \ddots & \vdots \\ 0 & \ddots & 2 & \ddots & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & \ddots & 0 \\ \vdots & \ddots & \ddots & \ddots & 2 & -1 \\ 0 & \cdots & \cdots & 0 & -1 & 1 \end{pmatrix}.$$

Define, for $i,j\in\{1,\dots,N\}$, $a_{ij} = \langle(\Gamma_1+L)^{-1}e_i,e_j\rangle$. By a direct symmetry argument, we have $a_{i,N-(j-1)} = a_{N-(i-1),j}$. Hence, the sets $\{j,N-(j-1)\}$ are set-admissible for every $j\in\{1,\dots,N\}$. Moreover, $\mathrm{Aut}(\mathscr{G}) = \{\mathrm{Id},\sigma\}$, where, for $i\in\{1,\dots,N\}$, $\sigma(i) = N-(i-1)$. Thus $(S_i) = (\{i,N-(i-1)\})_{i\in\{1,\lfloor N/2\rfloor\}}$ is a cluster admissible partition of $\{1,\dots,N\}$. Proposition 4.7 ensures cluster consensus for the partition $(S_i)_{i\in\{1,\lfloor N/2\rfloor\}}$.

Example 4.15 (Ring graph): Let $\tilde{L}$ be the $N\times N$ Laplacian matrix defined by

$$\tilde{L} = \begin{pmatrix} 2 & -1 & 0 & \cdots & 0 & -1 \\ -1 & 2 & \ddots & \ddots & \ddots & 0 \\ 0 & \ddots & 2 & \ddots & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & \ddots & 0 \\ 0 & \ddots & \ddots & \ddots & 2 & -1 \\ -1 & 0 & \cdots & 0 & -1 & 2 \end{pmatrix}.$$

In this case $\mathrm{Aut}(\mathscr{G})$ is isomorphic to the n-th diedral group D_n. In particular, given $i,j\in\{1,\dots,N\}$, there exists $\sigma\in\mathrm{Aut}(\mathscr{G})$ such that $j=\sigma(i)$. It follows that every subset of $\{1,\dots,N\}$ whose cardinality is equal to two is set-admissible. There exist more complex cluster admissible partitions which are due to symmetries of the coupling graph than in the case of Example 4.14 and they can be deduced by the study of the subgroups of D_n (see, for instance [9]). We propose to study explicitely the case $N=4$. In this case, the matrix $\gamma_1(\gamma_1+4\alpha)(\Gamma_1+L)^{-1}$ is equal to

$$\begin{pmatrix} \frac{\gamma_1^2+4\alpha\gamma_1+2\alpha^2}{\gamma_1+2\alpha} & \alpha & \frac{2\alpha^2}{\gamma_1+2\alpha} & \alpha \\ \alpha & \frac{\gamma_1^2+4\alpha\gamma_1+2\alpha^2}{\gamma_1+2\alpha} & \alpha & \frac{2\alpha^2}{\gamma_1+2\alpha} \\ \frac{2\alpha^2}{\gamma_1+2\alpha} & \alpha & \frac{\gamma_1^2+4\alpha\gamma_1+2\alpha^2}{\gamma_1+2\alpha} & \alpha \\ \alpha & \frac{2\alpha^2}{\gamma_1+2\alpha} & \alpha & \frac{\gamma_1^2+4\alpha\gamma_1+2\alpha^2}{\gamma_1+2\alpha} \end{pmatrix}.$$

We show easily that there is no set-admissible subsets of $\{1,\dots,4\}$ of cardinality 3, and that the cluster admissible partitions are $\{j,k\}\cup\{q,m\}$ for $j,k,q,m\in\{1,\dots,4\}$ pair-wise distinct, and $\{1,2,3,4\}$.

Now we adapt from [25, Section III.B] an example of synchronizable subset and admissible partition which is not due to a symmetry property of the coupling graph.

Example 4.16: Consider the following Laplacian matrix

$$\tilde{L} = \begin{pmatrix} 3 & -1 & 0 & -1 & -1 \\ -1 & 3 & -1 & 0 & -1 \\ 0 & -1 & 3 & -1 & -1 \\ -1 & 0 & -1 & 3 & -1 \\ -1 & -1 & -1 & -1 & 4 \end{pmatrix}.$$

We show that

$$(\Gamma_1+L)^{-1}(e_1+e_3+e_5) = \frac{1}{\gamma_1(\gamma_1+5\alpha)}\begin{pmatrix} \gamma_1+3\alpha \\ 3\alpha \\ \gamma_1+3\alpha \\ 3\alpha \\ \gamma_1+3\alpha \end{pmatrix}.$$

Hence the quantity $\langle(\Gamma_1+L)^{-1}(e_1+e_3+e_5),e_j\rangle$ does not depend on $j\in\{1,3,5\}$. By supplementary computations, one can show that the partition $\{1,3,5\}\cup\{2,4\}$ is cluster admissible. However, by cardinality considerations, $\{1,3,5\}$ cannot be an orbit of the action of a subgroup of $\mathrm{Aut}(\mathscr{G})$ on $\{1,\dots,5\}$, knowing that $|\mathrm{Aut}(\mathscr{G})| = 8$.

Remark 4.17: If both L_1 and L_2 are non zero, then we have to take into account two graphs $\mathscr{G}_1$ and $\mathscr{G}_2$. Every property remains true adding similar conditions on L_2, and considering synchronization properties both on the x_1 and x_2 coordinates.

B. Synchronization of all the subsystems towards the same steady state

We are interested in controlling the dynamics of the coupled system

$$\begin{aligned} \dot{x}_1 &= -(\Gamma_1+L_1)x_1 + uk_1q(x_2,\theta_2) \\ \dot{x}_2 &= -(\Gamma_2+L_2)x_2 + uk_2q(x_1,\theta_1) \end{aligned} \tag{8}$$

towards Φ_{01} or Φ_{10}. It corresponds to the control system (5) where $u_k^1 = u_k^2 \equiv u$ for every $k\in\{1,\dots,N\}$. The control u

is assumed to act identically on every sub-system of the network so that the control strategy acts symmetrically on the two proteins x_1 and x_2 involved in the system. Moreover, u satisfies the same hypothesis as in Appendix VI-A, that is, it depends only on the time $t \geq 0$ and on the regular domain to which the solution $x(t)$ of Equation (8) belongs. For this, we show that the control algorithm corresponding to the symmetric stabilization strategy exposed in Appendix VI-A can be adapted to this case, thanks to essential monotonicity properties of the dynamics which are presented in Section IV-B.1. Assume that the conditions (W) and (H) (see Appendix VI-A) hold.

1) Monotonicity properties of the coupled uncontrolled system: In the propositions 4.6 and 4.7, we have proved some synchronization properties of the dynamics when every subsystem has initial condition in B_{01} and B_{10}. In order to be able to prove our control strategy in Section IV-B.2, the next step is then to understand what happens if any subsystem belongs to B_{00}. Assume in this section that $L_1, L_2 \in \mathrm{Lap}_N(\mathbb{R})$ satisfy Assumption (W). By a slight abuse of notations, for $u = 1$, denote $(S)^{\pm} = (S_u)^{\pm}$, where $(S_u)^{\pm}$ is defined in Appendix VI-A. The main monotonicity result of this section is Proposition 4.22. It states that when every subsystem initially belongs to $(S)^+$ (respectively $(S)^-$) and satisfy some suitable supplementary assumptions, then the system converges to the full synchronized state Φ_{01} (respectively, Φ_{10}).

The next two lemmas are technical results concerning the monotonicity (see, for instance [22], [31]) of the semiflow for positive times of the two coordinates of Equation (8), when restricted to each regular domain, with respect to the natural partial order $\leq$ of $\mathbb{R}^N$. These results are useful in order to prove Proposition 4.22.

Definition 4.18: We say that a semiflow $(\phi_t)_{t\geq 0}$ on $\mathbb{R}^N$ is *monotone* if $x \leq y$ implies $\phi_t(x) \leq \phi_t(y)$ for every $t \geq 0$.

Lemma 4.19: For $b \in \mathbb{R}^N$, the semiflow of Equation

$$\dot{x} = -(\Gamma_j + L_j)x + b \tag{9}$$

is monotone, for $j \in \{1,2\}$.

Proof: Since L_j is a Laplacian matrix of a strongly connected graph, the off diagonal coefficients of $-(\Gamma_j + L_j)$ are positive for $j \in \{1,2\}$. Hence, Equation (9) is cooperative on $\mathbb{R}^N$. The result follows from [31, Chapter 3, Proposition 1.1]. ■

Remark 4.20: The matrix $-(\Gamma_j + L_j)$ being irreducible, the semiflow associated with Equation (9) is strongly monotone, in the sense defined in [31].

By the same argument, we obtain the following lemma.

Lemma 4.21: Consider $j \in \{1,2\}$ and $b_1, b_2 \in \mathbb{R}^N$ such that $b_2 \geq b_1$. For $k \in \{1,2\}$, let $y_k(t) \in \mathbb{R}^N$ be the solution of

$$\dot{x} = -(\Gamma_j + L_j)x + b_k \tag{10}$$

with initial condition $y_2(0) \geq y_1(0)$. Then $y_2(t) \geq y_1(t)$ for every $t \geq 0$.

We can deduce the following proposition.

Proposition 4.22: Let $x_0 \in (S)^- \times \cdots \times (S)^-$ (respectively, $x_0 \in (S)^+ \times \cdots \times (S)^+$). Assume that there exists $(\beta, \nu) \in (0, \theta_1) \times (0, \theta_2)$ such that $\beta \leq x_{1,k}(0)$ and $\nu \geq x_{2,k}(0)$ for every $k \in \{1, \ldots, N\}$, and $(\beta, \nu) \in (S)^-$ (respectively, $\beta \geq x_{1,k}(0)$ and $\nu \leq x_{2,k}(0)$ for every $k \in \{1, \ldots, N\}$, and $(\beta, \nu) \in (S)^+$). Then the solution $x(t)$ of Equation (2) such that $x(0) = x_0$ reaches $B_{10} \times \cdots \times B_{10}$ (respectively, $B_{01} \times \cdots \times B_{01}$) in finite time.

Proof: In this proof, the inequalities between vectors of $\mathbb{R}^N$ are taken in the sense of the natural partial order of $\mathbb{R}^N$, i.e. they are taken component by component.

Let $x_0 \in (S)^- \times \cdots \times (S)^-$ and consider the solution $x(t)$ of Equation (2) such that $x(0) = x_0$.

We start the proof by showing that Lemma 4.19 is sufficient to prove that one subsystem changes regular domain from B_{00} to B_{10}. Then, successive applications of Lemma 4.21 show by induction that the other subsystems undergo the same changes of regular domains.

Define $(\beta, \nu) \in (0, \theta_1) \times (0, \theta_2)$ as in the claim of the lemma, and the solution $\bar{x}(t)$ of Equation (2) such that $\bar{x}_{1,k}(0) = \beta$, and $\bar{x}_{2,k}(0) = \nu$ for every $k \in \{1, \ldots, N\}$. Notice that $\bar{x}(t)$ satisfies the equation

$$\begin{aligned} \tfrac{d}{dt}\bar{x}_1 &= -\Gamma_1 \bar{x}_1 + k_1 q(\bar{x}_2, \theta_2) \\ \tfrac{d}{dt}\bar{x}_2 &= -\Gamma_2 \bar{x}_2 + k_2 q(\bar{x}_1, \theta_1), \end{aligned} \tag{11}$$

that is, the non-coupled equation, and we have for every $k, k' \in \{1, \ldots, N\}$ and $j \in \{1,2\}$, $\bar{x}_{j,k}(t) = \bar{x}_{j,k'}(t)$, for every $t \geq 0$. By definition of the separatrix (S) defined in Appendix VI-A.1, we have, for every $t > 0$, $\bar{x}_{2,k}(t) \leq \theta_2 - C$ with $C > 0$, and there exists $t > 0$ such that $\bar{x}_{1,k}(t) = \theta_1$, for every $k \in \{1, \ldots, N\}$. Let $T_1 = \inf\{t > 0,\ \exists j \in \{1, \ldots, N\} \mid x_{1,j}(t) = \theta_1\}$ and $T_2 = \inf\{t > 0,\ \exists j \in \{1, \ldots, N\} \mid x_{2,j}(t) = \theta_2\}$. Applying Lemma 4.19 to the equations $\dot{x}_1 = -(\Gamma_1 + L_1)x_1 + k_1 q(\pi_2(B), \theta_2)$ and $\dot{x}_2 = -(\Gamma_2 + L_2)x_2 + k_2 q(\pi_1(B), \theta_1)$, where $B = B_{00} \times \cdots \times B_{00}$, we get $x_1(t) \geq \bar{x}_1(t)$ and $x_2(t) \leq \bar{x}_2(t)$ for every $t < \min(T_1, T_2)$. Hence we can deduce that T_1 is finite and $T_1 < T_2$. We can assume that $x_{1,k_1}(T_1) = \theta_1$, where $k_1 \in \{1, \ldots, N\}$, and for every $k \neq k_1$, $x_{1,k}(T_1) < \theta_1$. Assumption (W) guarantees that $(x_{1,k_1}, x_{2,k_1})(t) \in B_{10}$ for $t > T_1$. Moreover, for every $k \neq k_1$, $(x_{1,k}, x_{2,k})(T_1) \in (S)^-$, and $x_1(T_1) \geq \bar{x}_1(T_1)$ and $x_2(T_1) \leq \bar{x}_2(T_1)$. At time $t_1 = T_1 + \varepsilon$ with $\varepsilon > 0$ small enough, we have $(x_{1,k_1}, x_{2,k_1})(t_1) \in B_{10}$, $(x_{1,k}, x_{2,k})(t_1) \in B_{00}$ for $k \neq k_1$, and $x_1(t_1) \geq \bar{x}_1(t_1)$, $x_2(t_1) \leq \bar{x}_2(t_1)$.

Assume now that a subset S of subsystems of cardinality $\#S \geq 1$ belong to B_{10} and other subsystems belong to B_{00} at a time $T \geq t_1$, and that $\bar{x}_1(T) \leq x_1(T)$, $\bar{x}_2(T) \geq x_2(T)$. Denote the regular domain to which $x(T)$ belongs by $\tilde{B}$. Consider Equation (2) restricted to the domain B, that is,

$$\begin{aligned} \tfrac{d}{dt}x_1 &= -(\Gamma_1 + L_1)x_1 + k_1 q(\pi_2(\tilde{B}), \theta_2) \\ \tfrac{d}{dt}x_2 &= -(\Gamma_2 + L_2)x_2 + k_2 q(\pi_1(\tilde{B}), \theta_1). \end{aligned} \tag{12}$$

By definition of $\tilde{B}$, we obtain $q(\pi_1(\tilde{B}), \theta_1) \geq q(\bar{x}_1(t), \theta_1)$ and $q(\pi_2(\tilde{B}), \theta_2) \leq q(\bar{x}_2(t), \theta_2)$, for every $t \geq T_1$, until $\bar{x}(t)$ reaches the frontier of $B = B_{00} \times \cdots \times B_{00}$. Applying Lemma 4.21 to both x_1 and x_2 coordinates of the solutions of the equations (2) and (12) with initial conditions, respectively, $\bar{x}(T)$ and $x(T)$, we obtain $x_1(t) \geq \bar{x}_1(t)$ and $x_2(t) \leq \bar{x}_2(t)$ for $t \geq T$, until the trajectory $x(t)$ reaches the frontier of $\tilde{B}$. Using the fact that for every $t>0$, $\bar{x}_2(t) \leq \theta_2 - C$ with $C>0$, and the existence of $t>0$ such that $\bar{x}_1(t) = \theta_1$, we deduce that there exist $\tilde{T} > T$ and $\tilde{k} \in \{1,\ldots,N\} \setminus S$ such that $x_{1,\tilde{k}}(\tilde{T}) = \theta_1$. Furthermore, Assumption (W) guarantees that $(x_{1,\tilde{k}}, x_{2,\tilde{k}})(t) \in B_{10}$ for $t > \tilde{T}$, and we have $x_1(\tilde{T}) \geq \bar{x}_1(\tilde{T})$ and $x_2(T_2) \leq \bar{x}_2(\tilde{T})$. Hence, at a time $\tilde{t}_1 = \tilde{T} + \varepsilon$, with $\varepsilon > 0$ small enough, $\#S+1$ subsystems belong to B_{10} and we have $\bar{x}_1(\tilde{t}_1) \leq x_1(\tilde{t}_1)$, $\bar{x}_2(\tilde{t}_1) \geq x_2(\tilde{t}_1)$.

We have proved by induction that every subsystem reaches the regular domain B_{10} in finite time, and that $\bar{x}_1(t) \leq x_1(t)$, $\bar{x}_2(t) \geq x_2(t)$, for every $t \geq 0$. A similar reasoning holds when $x_0 \in (S)^+ \times \cdots \times (S)^+$, where the inequality $\bar{x}_1(t) \geq x_1(t)$, $\bar{x}_2(t) \leq x_2(t)$ holds for every $t \geq 0$.

■

2) Control Algorithm: Let $u_{\min}^{01}, u_{\min}^{10}, u_{\max}$ be chosen as in Appendix VI-A. By an immediate adaptation of Equation (3) to the controlled case, the focal points of Equation (8) are given by

$$\begin{aligned} \bar{x}_1 &= uk_1(\Gamma_1 + L_1)^{-1} q(\pi_2(B), \theta_2) \\ \bar{x}_2 &= uk_2(\Gamma_2 + L_2)^{-1} q(\pi_1(B), \theta_1). \end{aligned} \tag{13}$$

By a direct study of Equation (13), we have the following lemma.

Lemma 4.23: Every focal point of Equation (8) with $u \equiv u_{\min}^{01}$ (respectively, $u_{\min}^{01}$) belongs to $B_{00} \times \cdots \times B_{00}$.

- **First step:** Choose $u \equiv u_{\min}^{01}$ (respectively, $u_{\min}^{01}$). By Lemma 4.23, every subsystem of the network reaches the domain B_{00} in finite time. We obtain the following.
  Proposition 4.24: The solution $x(t)$ of Equation (8) when $u \equiv u_{\min}^{01}$ (respectively, $u \equiv u_{\min}^{10}$) converges when $t \to \infty$ to the synchronized state $\Phi^* = (\bar{x}_1, \bar{x}_2)$ defined by $\bar{x}_{1,k} = u_{\min}^{01} \frac{k_1}{\gamma_1}$, and $\bar{x}_{2,k} = u_{\min}^{01} \frac{k_2}{\gamma_2}$ (respectively, $\bar{x}_{1,k} = u_{\min}^{10} \frac{k_1}{\gamma_1}$, and $\bar{x}_{2,k} = u_{\min}^{10} \frac{k_2}{\gamma_2}$) for every $k \in \{1,\ldots,N\}$.
  Fix $\varepsilon > 0$ small enough. Lemma 4.24 allows to consider $T_\varepsilon > 0$ such that for every initial condition $x_0 \in K^N$, the solution of Equation (8) such that $x(0) = x_0$ satisfies $||x(T_\varepsilon) - \Phi^*|| < \varepsilon$, that is, every subsystem of the network can be driven to an arbitrary small neighborhood of $(u_{\min}^{01} \frac{k_1}{\gamma_1}, u_{\min}^{01} \frac{k_2}{\gamma_2})$ (respectively, $(u_{\min}^{10} \frac{k_1}{\gamma_1}, u_{\min}^{10} \frac{k_2}{\gamma_2})$). In particular, one can choose $\varepsilon > 0$ small enough to guarantee the existence of $(\beta, \nu) \in (0,\theta_1) \times (0,\theta_2)$ such that $\beta \leq x_{1,k}(T_\varepsilon)$ and $\nu \geq x_{2,k}(T_\varepsilon)$ for every $k \in \{1,\ldots,N\}$, and $(\beta,\nu) \in (S_{u_{\max}})^-$, as in Proposition 4.22.
- **Second step:** For $t \geq T_\varepsilon$, choose $u \equiv u_{\max}$. Using Proposition 4.22, one can prove the following result.
  Proposition 4.25: Assume that u is defined as in the two steps above. Then the solution $x(t)$ of Equation (8) reaches the regular domain $B_{01} \times \cdots \times B_{01}$ (respectively, $B_{10} \times \cdots \times B_{10}$) in finite time.
- **Third step:** When every subsystem has reached B_{01} (respectively, B_{10}), choose $u \equiv 1$. A direct consequence of Proposition 4.6 is the following.
  Theorem 4.26: Assume that u is defined as in the three steps above. Then the solution $x(t)$ of Equation (8) converges to Φ_{01} (respectively, Φ_{10}) when $t \to \infty$, uniformly w.r.t. the initial condition $x_0 \in K^N$.

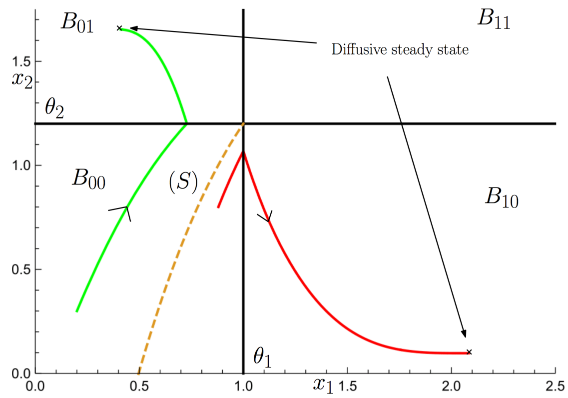
3) Simulations: Consider the following piecewise-affine differential system in $\mathbb{R}^4$,

$$\begin{aligned} \dot{x}_{1,1} &= -\gamma_1 x_{1,1} + k_1 u s^-(x_{2,1}, \theta_2) + a_1(x_{1,2} - x_{1,1}) \\ \dot{x}_{2,1} &= -\gamma_2 x_{2,1} + k_2 u s^-(x_{1,1}, \theta_1) + a_2(x_{1,1} - x_{1,2}) \\ \dot{x}_{1,2} &= -\gamma_1 x_{1,2} + k_1 u s^-(x_{2,2}, \theta_2) + a_1(x_{1,1} - x_{1,2}) \\ \dot{x}_{2,2} &= -\gamma_2 x_{2,2} + k_2 u s^-(x_{1,2}, \theta_1) + a_2(x_{1,2} - x_{1,1}), \end{aligned} \tag{14}$$

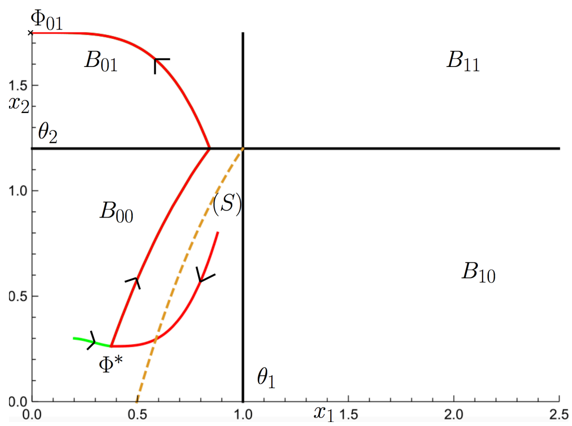
where, $(\gamma_j)_{j\in\{1,2\}}$, $(k_j)_{j\in\{1,2\}}$ are positive constants satisfying Assumption (H), and $a_1 \geq 0$ (respectively, $a_2 \geq 0$) are the diffusion couplings on the x_1-coordinates (respectively, the x_2-coordinates), that are chosen as $a_1 = a_2 = 0.05$. We have made simulations of such a system with $(\gamma_1,\gamma_2) = (0.2, 0.8)$, $(k_1,k_2) = (0.5, 1.4)$, $(\theta_1,\theta_2) = (1, 1.2)$, and further simulations are made with the same parameters. Notice that Assumption (W) is satisfied with this choice of parameters, and the value of $u_{\max}$ in the control algorithm IV-B.2 can be chosen as $u_{\max} = 1$. One can choose $u_{\min}^{01} = 0.1$, $u_{\min}^{10} = 0.3$, and the time T_ε of the second phase of the control strategy is chosen as $T_\varepsilon = 20$. Consider the initial conditions: $(x_{1,1}(0), x_{2,1}(0)) = (0.5, 1.3)$, and $(x_{1,2}(0), x_{2,2}(0)) = (0.8, 0.3)$. Figure 3(a) illustrates the convergence of $x(t)$ towards a diffusive steady state for the uncontrolled system $u \equiv 1$. The trajectory $(x_{1,1}(t), x_{2,1}(t))$ of the first subsystem is plotted in red and the trajectory $(x_{1,2}(t), x_{2,2}(t))$ of the second subsystem is plotted in green. The dashed line $(S) = (S_{u_{\max}})$ represents the separatrix, as defined in Appendix VI-A. Figure 3(b) illustrates the convergence of $x(t)$ towards Φ_{01} for the controlled system. Figure 3(c) illustrates the convergence of $x(t)$ towards Φ_{10} for the controlled system. We notice that after the first phase of the control strategy, that is the phase during which the two systems converge towards Φ^*, the two systems (red and green curves) follow very close trajectories.

C. Synchronization of cluster states

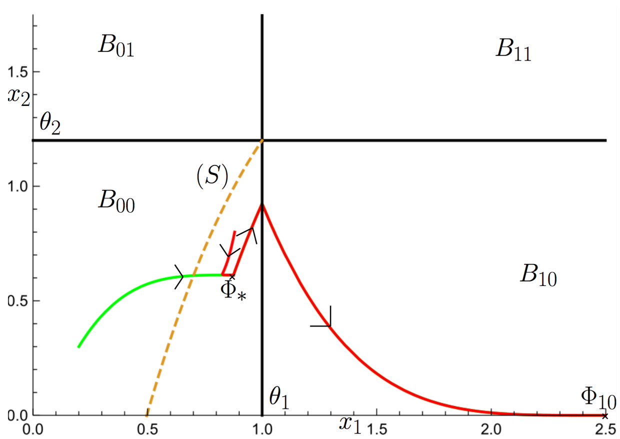
Assume that the coupling acts only on the x_1-coordinates, that is, $L_2 = 0$. Assume moreover that Condition (W) holds, that the condition $\theta_j < \frac{k_j}{\gamma_j}$, $j \in \{1,2\}$ is satisfied as in Appendix VI-B, and let $(S_j)_{j\in\{1,\ldots,k\}}$ be a cluster admissible partition associated with the graph corresponding to the Laplacian matrix L_1, as defined in Definition 4.5. Here we propose a control strategy which ensures synchronization of subsystems belonging to S_j, for every $j \in \{1,\ldots,k\}$, inspired by the individual asymmetric stabilization strategy presented in Appendix VI-B. Assume that our goal is to synchronize the subsystems belonging to S_j in the regular domain B_{η_j}, where, for every $j \in \{1,\ldots,k\}$, $\eta_j = 10$ or 01, is fixed. Notice that in this case, one needs to separate two sets of subsystems in the domains B_{01} and B_{10}. In order to get this, one could first imagine adapting the symmetric control algorithm exposed in Section IV-B.2 by acting on the two sets by a symmetric control strategy, that is, choosing $u_j^1 = u_j^2 \equiv u$ for j such that $\eta_j = 10$ and $u_j^1 = u_j^2 \equiv v$ for j such that $\eta_j = 01$, where $u : \mathbb{R} \to \mathbb{R}$ and $v : \mathbb{R} \to \mathbb{R}$ are independent controls. However, in this case, no monotonicity argument similar to those used in Section IV-B.1 can be used, and thus one needs to use an asymmetric control strategy, by acting



(a) Convergence towards a diffusive steady state for the uncontrolled system.



(b) Convergence towards Φ_{01} for the controlled system



(c) Convergence towards Φ_{10} for the controlled system

Fig. 3. Symmetric control strategy for full synchronization

separately on the x_1 and x_2-coordinates of the system. Our control method then requires both to be able to distinguish the proteins quantities x_1 and x_2 and to select cells (that is, subsystems) in which we modify the production rates of such proteins. Assume that we have a control $u:\mathbb{R}\to\mathbb{R}$ acting on the systems, such that for $k\in S_i$, the k-th subsystem is controlled as:

$$\begin{array}{l}\dot{x}_{1,k} = -\gamma_1 x_{1,k} + u^1_{\eta_i}(t) k_1 s^-(x_{2,k},\theta_2) + \sum_{j=1}^N l_{kj}(x_{1,j}-x_{1,k})\\ \dot{x}_{2,k} = -\gamma_2 x_{2,k} + u^2_{\eta_i}(t) k_2 s^-(x_{1,k},\theta_1),\end{array} \tag{15}$$

where $j_i\in\{1,2\}$ only depends on S_i, and $(u^1_{10},u^2_{10})=(1,u)$, $(u^1_{01},u^2_{01})=(1,u)$. Notice that the control system depends on the cluster admissible partition $(S_j)_{j\in\{1,\ldots,k\}}$. We are going to see that our control strategy only allows to converge towards arbitrary steady states of Equation (6), while in Section IV-B, the control strategy only allowed us to choose between the full synchronized steady states Φ_{01} and Φ_{10}.

By Assumption (W) and a continuity argument of the focal points of Equation (15) w.r.t. u at $u=0$, where u is seen as a parameter which is independent of t, we get the following lemma.

Lemma 4.27: For $u\equiv u_{\min}<\min(\frac{\gamma_1\theta_1}{k_1},\frac{\gamma_2\theta_2}{k_2})$ small enough, every focal point $\bar{x}$ of Equation (15) is such that $\bar{x}_{1,k}<\theta_1$ and $\bar{x}_{2,k}>\theta_2$ for $k\in S_i$ such that $\eta_i=10$ (respectively, $\bar{x}_{1,k}>\theta_1$ and $\bar{x}_{2,k}<\theta_2$ for $k\in S_i$ such that $\eta_i=01$).

Notice that the coupling terms impose a more restrictive condition on $u_{\min}$ in Lemma 4.27 than those used in the control strategy of the individual system proposed in Appendix VI-B. This condition depends on the coupling graph associated to L_1 and it seems to be a hard task to express it explicitely.

Now we can present the following control algorithm for cluster synchronization.

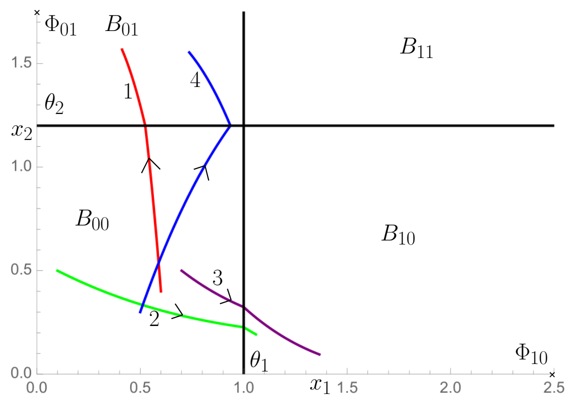
1) Control algorithm::

- **First step:** Choice of the regular domain. A consequence of Lemma 4.27 is the following.
  Proposition 4.28: Choose $u\equiv u_{\min}$, where $u_{\min}$ is small enough, as previously. Then the solution $x(t)$ of Equation (15) is such that for every i and $j\in S_i$, the subsystem $(x_{1,j}(t),x_{2,j}(t))$ reaches the regular domain B_{η_i} in finite time.
  Denote the time at which every system of $\{1,\ldots,N\}$ has reached its corresponding regular domain B_{η_i} by T_1.
- **Second step:** For $t\geq T_1$, choose $u_1=u_2\equiv 1$. Applying Proposition 4.7, we get the following result.
  Theorem 4.29: Assume that u is defined as in the two steps above. Then for every $i\in\{1,\ldots,k\}$, there exists $\bar{x}_i\in B_{\eta_i}$ such that for every $j\in S_i$, $(x_{1,j}(t),x_{2,j}(t))\to\bar{x}_i$ when $t\to+\infty$, uniformly w.r.t. the initial condition $x_0\in K^N$.

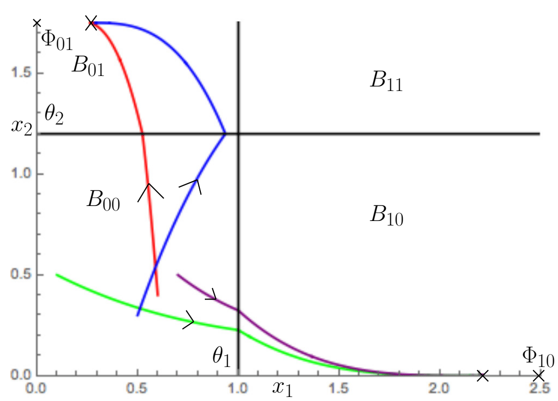
Remark 4.30:
- A similar control stategy would be valid also in the case where the coupling acts also on the x_2-coordinates, that is $L_2\neq 0$, taking into account synchronization on the two coordinates separately, as already noticed in Remark 4.17.
- By a continuity argument w.r.t. parameters of the dynamics, up to increasing the times of the first and second steps of the control algorithm of Section IV-B.2, and the time of the first step of the control algorithm of Section IV-C, the proposed control strategies are robust w.r.t. variations of the coefficients of the coupling matrix L. That is, the trajectories converge to the

desired targets, uniformly w.r.t. possible uncertainities of the coefficients of the coupling matrix L belonging to compact intervals such that Assumption (W) is satisfied for L (see Remark 4.2).

2) Simulations: Consider the example of the chain graph as in Remark 4.14 with $N = 4$. We illustrate on Figure 4 the synchronization of subsystems 1 and 4 and subsystems 2 and 3, by implementing a control strategy as in Section IV-C. We illustrate on Figure 5 the synchronization of subsystems 1 and 4 and subsystems 2 and 3, by plotting the quadratic difference of their first components. We illustrate on Figure 6(a) the failure of synchronization of subsystems 1 and 2. We illustrate on Figure 6(b) the synchronization of subsystems 1 and 2 using the control strategy of Section IV-C, when the graph is a ring as in Remark 4.15 with $N = 4$. On every figure, subsystem 1 is in red, subsystem 2 is in green, subsystem 3 is in purple and subsystem 4 is in blue, that is, we have plotted the trajectories $(x_{1,k}(t), x_{2,k}(t))$ in these different colors for $k \in \{1, \ldots, 4\}$.



(a) First phase of the control algorithm subsystem 1 in red, subsystem 2 in green, subsystem 3 in purple and subsystem 4 in blue.

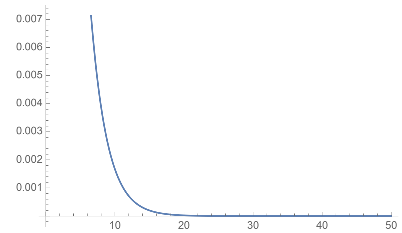


(b) Full control algorithm

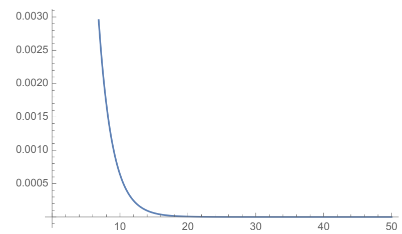
Fig. 4. Control strategy for synchronization in the chain case in the weak coupling regime

V. Homogeneous strong coupling behavior

In this section we study the dynamical and control properties of the coupled system (5) when the weak coupling condition is not satisfied, and every coupling term is large

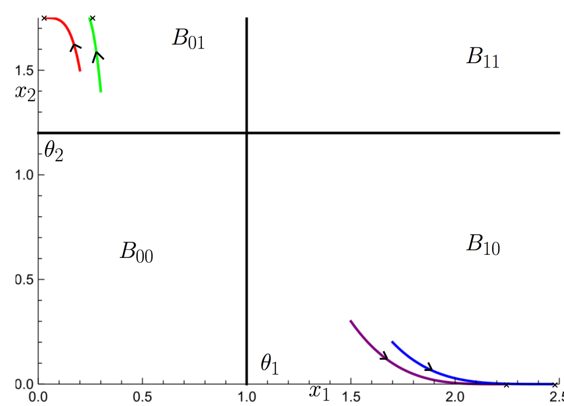


(a) Quadratic difference between the first component of subsystems 1 and 4 during the second phase of the control algorithm, as a function of time.

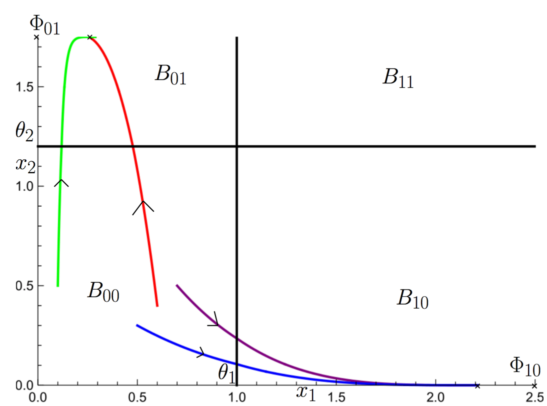


(b) Quadratic difference between the first component of subsystems 2 and 3 during the second phase of the control algorithm, as a function of time.

Fig. 5. Synchronization of the subsystems 1 and 4, and 2 and 3.



(a) Failure of synchronization between subsystems 1 and 2 for the chain case



(b) Control strategy for synchronization between subsystems 1 and 2 for the ring case

Fig. 6. Comparison of the chain and ring cases in the weak coupling regime

enough. In this regime, called *homogeneous strong coupling regime* we will see that it is sufficient to control a subset of the subsystems to the desired regular domain in order to induce the full coupled system to synchronize there. Moreover the proposed control strategy does not depend on the coupling graph topology.

A. Strong coupling uncontrolled dynamics

Assume in this section that only the x_1-coordinates are coupled with an homogeneous strength $\alpha > 0$ so that the system (2) writes

$$\begin{aligned}\dot{x}_1 &= -(\Gamma_1 + \alpha L_1)x_1 + k_1 q(x_2, \theta_2)\\ \dot{x}_2 &= -\Gamma_2 x_2 + k_2 q(x_1, \theta_1).\end{aligned} \tag{16}$$

Recall that for a regular domain B of K^N, the corresponding focal point is given by

$$\begin{aligned}\bar{x}_1(\alpha, B) &= k_1(\Gamma_1 + \alpha L_1)^{-1} q(\pi_2(B), \theta_2)\\ \bar{x}_2(B) &= k_2 \Gamma_2^{-1} q(\pi_1(B), \theta_1).\end{aligned} \tag{17}$$

Lemma 5.1: Let L be a $N \times N$ symmetric Laplacian matrix of a strongly connected graph $\mathscr{G}$. Then

$$(I + \alpha L)^{-1} \to \frac{1}{N}\begin{pmatrix}1 & \cdots & 1\\ \vdots & \cdots & \vdots\\ 1 & \cdots & 1\end{pmatrix}$$

when $\alpha \to +\infty$.

Proof: Under the assumption of strong connectedness of $\mathscr{G}$, the multiplicity of the zero eigenvalue of L is equal to 1 and its associated eigenvector is $\sum_{j=1}^{N} e_j$. Moreover, the eigenvalues of $(I+\alpha L)^{-1}$ are defined as $\mu_j = \frac{1}{1+\alpha\lambda_j}$ for $j \in \{1,\ldots,N\}$, where $(\lambda_j)_{j\in\{1,\ldots,N\}}$ are the eigenvalues of the symmetric matrix L. The result follows by diagonalization of L. ∎

Next proposition follows from Lemma 5.1. It states that the x_1-coordinates of the focal points of Equation (16) tend to a regular subdivision of the interval $(0, \frac{k_1}{\gamma_1})$ when $\alpha \to +\infty$, the focal points being cartesian products of the points $\left(\frac{jk_1}{\gamma_1}, \frac{k_2}{\gamma_2}\right)$ and $\left(\frac{jk_1}{\gamma_1}, 0\right)$.

Proposition 5.2: Define the matrix $P = \frac{k_1}{\gamma_1 N}\begin{pmatrix}1 & \cdots & 1\\ \vdots & \cdots & \vdots\\ 1 & \cdots & 1\end{pmatrix}$. For every regular domain B of K^N, we have $\bar{x}_1(\alpha, B) \to Pq(\pi_2(B), \theta_2)$ when $\alpha \to +\infty$, where $\bar{x}_1(\alpha, B)$ is given by Equation (17).

Assume that a number $j \in \{0,\ldots,N\}$ of subsystems have a x_2-coordinate smaller that θ_2. Then Proposition 5.2 states that every subsystem has its x_1-coordinate which converges towards a point that is close to $\frac{jk_1}{N\gamma_1}$ for a large α and $t \to +\infty$, and its x_2-coordinate converges towards 0 or $\frac{k_2}{\gamma_2}$. In order to illustrate this essential feature, we have plotted on Figure 7, in the case $N = 7$, the limit of the x_1-coordinate $\bar{x}_{1,k}(+\infty, B)$ of a focal point corresponding to a domain B such that 2 subsystems have a x_2-coordinate strictly smaller that θ_2. In this case, subsystems having a x_1-coordinate which is smaller that θ_1 converge towards the upper blue cross, while other subsytems converge towards the lower blue cross. The coordinates of other focal points are represented by black crosses.

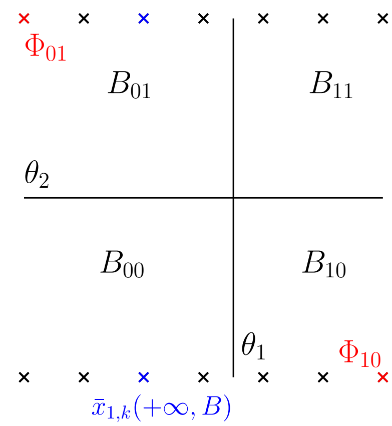


Fig. 7. Limit repartition of the focal points when $\alpha \to +\infty$, when $N = 7$.

Define the set $\mathscr{S} = \{\frac{jk_1}{N\gamma_1}, j \in \{0,\ldots,N\}\}$, and introduce the following condition

$$\theta_1 \notin \mathscr{S} \tag{A}$$

Proposition 5.3 (Lower coupling bound): Assume that Condition (A) holds. Then there exists $\alpha_s > 0$ such that for $\alpha \geq \alpha_s$, the only steady states of Equation (17) are the synchronized steady states Φ_{01} and Φ_{10}.

Proof: By Proposition 5.2, there exists α_s such that for $\alpha \geq \alpha_s$ and every regular domain B, we have $\bar{x}_{1,k}(\alpha, B) < \theta_1$ for every $k \in \{1,\ldots,N\}$, or $\bar{x}_{1,k}(\alpha, B) > \theta_1$ for every $k \in \{1,\ldots,N\}$. In particular, the only steady states of Equation (16) are the synchronized steady states Φ_{01} and Φ_{10}. ∎

Definition 5.4: We say that the dynamics of Equation (16) is studied in the *strong coupling* regime when $\alpha \geq \alpha_s$.

Remark 5.5:
- The value of α_s depends on the coupling graph $\mathscr{G}$ and can be computed explicitely by linear algebra computations.
- Proposition 5.3 is true because the systems that we are coupling are identical, else the asymptotic expansion of $\bar{x}_1(\alpha, B)$ made in Proposition 5.2 is no more true.
- If Condition (A) is not satisfied, steady states having coordinates belonging to the threshold lines may persist even when α is increasing, as it has already been noticed in [7].

Consider $C_{\text{sync}} = \lfloor \frac{\theta_1 N \gamma_1}{k_1} \rfloor \in \{0,\ldots,N-1\}$. Assume $\alpha \geq \alpha_s$, where α_s is defined as in Proposition 5.3. Let $x(t)$ be the solution of Equation (16), and denote the cardinality of the set $\{i \in \{1,\ldots,N\} \mid (x_{1,i}(t), x_{2,i}(t)) \in B_{kj}\}$ at time $t \geq 0$ by $P_{kj}(t)$, for $k, j \in \{0,1\}$.

Proposition 5.6: Assume that Condition (A) holds, and $P_{01}(0) \geq N - C_{\text{sync}}$. Then $x(t)$ converges to Φ_{01} when $t \to +\infty$.

Proof: Let B be the regular domain of K^N such that $x(0) \in B$, and $\alpha \geq \alpha_s$. By Proposition 5.2, the condition $P_{01}(0) \geq N - C_{\text{sync}}$ implies that the corresponding focal point $(\bar{x}_1(\alpha,B),\bar{x}_2)$, defined as in Equation (17), satisfies $\bar{x}_{1,k}(\alpha,B) < \theta_1$ for every $k \in \{1,\dots,N\}$.

We claim that there exists a time $T_1 > 0$ and $j \in \{1,\dots,N\}$ such that the j-th subsystem reaches the frontier between $B_{00} \cup B_{10} \cup B_{11}$ and B_{01} at time T_1, and $P_{01}(T_1) \geq N - C_{\text{sync}}$. Indeed, under the condition $\bar{x}_{1,k}(\alpha,B) < \theta_1$ for every $k \in \{1,\dots,N\}$, the subsystems initially in B_{10} can only reach B_{00}, those in B_{00} can only reach B_{01}, and those in B_{11} can reach B_{01} or B_{10}, while subsystems initially in B_{01} remain in B_{01}. We get the result by induction, noticing that after each change of regular domain $B \mapsto \tilde{B}$ for $x(t)$, the previous properties imply that the condition $P_{01} \geq N - C_{\text{sync}}$ remains true. Hence the focal point $(\bar{x}_1(\alpha,\tilde{B}),\bar{x}_2(\tilde{B}))$ corresponding to the regular domain $\tilde{B}$ satisfies $\bar{x}_{1,k}(\alpha,\tilde{B}) < \theta_1$ for every $k \in \{1,\dots,N\}$.

■

By a similar argument, we get the following property.

Proposition 5.7: Assume that Condition (A) holds, and $P_{10}(0) > C_{\text{sync}}$. Then $x(t)$ converges to Φ_{10} when $t \to +\infty$.

Inspired by works in the smooth case (see, for instance [26], [12]), we conjecture that under Condition (A), for every $\alpha \geq \alpha_s$, the solution $x_\alpha(t)$ of Equation (16) satisfies $x_\alpha(t) \to \Phi_{10}$ or Φ_{01} when $t \to +\infty$.

B. Control strategy

Assume that Assumption (A) holds. We are going to see that we can force the system to converge towards Φ_{10} or Φ_{01}, by applying a control on a strict subset of subsystems.

Consider $\alpha \geq \alpha_s$, where α_s is defined in Proposition 5.3, that is, the dynamics is studied in the homogeneous strong coupling regime.

1) Control towards Φ_{10}: Let S be a subset of $\{1,\dots,N\}$ having cardinality strictly larger than C_{sync}. Assume that we have a control $u_2 : \mathbb{R} \to \mathbb{R}$ acting on the systems belonging to S, such that for $k \in \{1,\dots,N\}$, the k-th subsystem is controlled as:

$$\begin{array}{l} \dot{x}_{1,k} = -\gamma_1 x_{1,k} + k_1 s^-(x_{2,k},\theta_2) + \alpha \sum_{j=1}^N l_{kj}(x_{1,j} - x_{1,k}) \\ \dot{x}_{2,k} = -\gamma_2 x_{2,k} + k_2 v_k(t) s^-(x_{1,k},\theta_1), \end{array} \tag{18}$$

where $v_k = u_2$ is $k \in S$, else $v_k \equiv 1$.

We propose the following control algorithm, which stabilizes the system in the full synchronized steady state Φ_{10} when $t \to \infty$.

Control algorithm:

- **First step:** Choose $u_2 \equiv u_{\min} < \frac{\theta_2\gamma_2}{k_2}$ for $t \in (0,T)$, where $T > 0$ is defined as follows.
  A direct study of the focal points shows that there exists $T_1 > 0$ such that, for every $j \in S$, $(x_{1,j}(T_1),x_{2,j}(T_1)) \in B_{10} \cup B_{00}$. Let B be the regular domain of K^N such that $x(T_1) \in B$. We have $P_{00}(T_1) + P_{10}(T_1) > C_{\text{sync}}$. Hence, by definition of the focal points (see Equation (17)), we have $\bar{x}_1(\alpha,B) > \theta_1$, where the inequality is taken component by component. Moreover, the components of $\bar{x}_2(B)$ corresponding to the subsystems belonging to S are smaller than θ_2 because $u_{\min} < \frac{\theta_2\gamma_2}{k_2}$. By induction, there exists $T > 0$ such that, for every $j \in S$, $(x_{1,j}(T),x_{2,j}(T)) \in B_{10}$.
- **Second step:** Choose $u_2 \equiv 1$ for $t \geq T$. Applying Proposition 5.7, we get that the solution $x(t)$ of Equation (18) converges to Φ_{10} when $t \to +\infty$.

2) Control towards Φ_{01}: Choose S having cardinality larger than $N - C_{\text{sync}}$. Assume that we have a control $u_1 : \mathbb{R} \to \mathbb{R}$ acting on the systems, such that for $k \in \{1,\dots,N\}$, the k-th subsystem is controlled as:

$$\begin{array}{l} \dot{x}_{1,k} = -\gamma_1 x_{1,k} + v_k(t) k_1 s^-(x_{2,k},\theta_2) + \alpha \sum_{j=1}^N l_{kj}(x_{1,j} - x_{1,k}) \\ \dot{x}_{2,k} = -\gamma_2 x_{2,k} + k_2 s^-(x_{1,k},\theta_1), \end{array} \tag{19}$$

where $v_k = u_1$ is $k \in S$, else $v_k \equiv 1$. We propose the following control algorithm, which stabilizes the system in the full synchronized steady state Φ_{01} when $t \to \infty$.

Control algorithm:

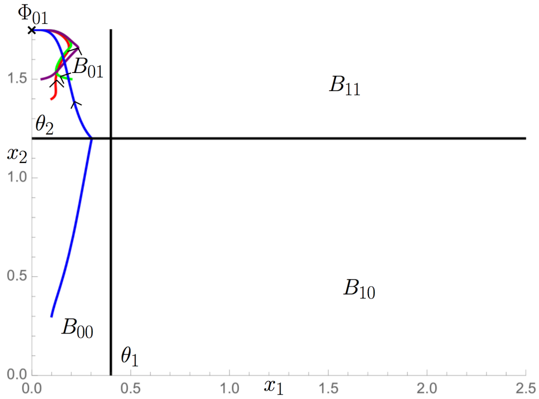
- **First step:** Choose $u_1 \equiv u_{\min} \in \left(0, 1 - \frac{N}{\#S}\left(1 - \frac{\theta_1\gamma_1}{k_1}\right)\right)$ for $t \in (0,T)$, where $T > 0$ is such that for every $j \in S$, $(x_{1,j}(T),x_{2,j}(T)) \in B_{01}$.
- **Second step:** Choose $u_1 \equiv 1$ for $t \geq T$. Applying Proposition 5.6, we get that the solution $x(t)$ of Equation (19) converges to Φ_{01} when $t \to \infty$.

Remark 5.8: The upper bound for $u_{\min}$ comes from the fact that the diffusion acts on the x_1-coordinates. Indeed, a similar study of the focal points as made in Proposition 5.2 shows that the corresponding focal point $(\bar{x}_1(\alpha),\bar{x}_2)$ is such that $\bar{x}_1(\alpha) \to k_1\left(\frac{u_{\min}\#S + N - \#S}{\gamma_1 N}\right)$, when $\alpha \to \infty$. The upper bound for $u_{\min}$ follows from the condition $k_1\left(\frac{u_{\min}\#S+N-\#S}{\gamma_1 N}\right) < \theta_1$. It depends on the cardinality of S in the sense that the more numerous the controlled subsystems are, the less restrictive it is. In particular, if $\#S = N$, then there is no constraint except $u_{\min} < \frac{\theta_1\gamma_1}{k_1}$.

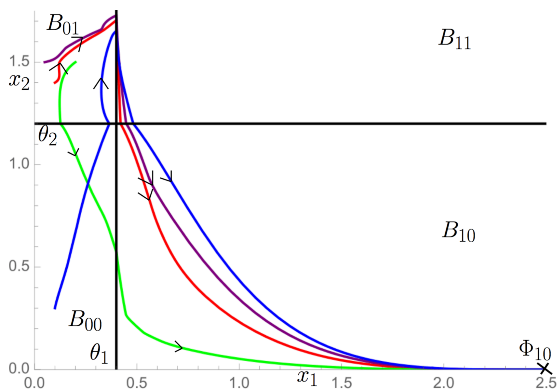
Remark 5.9:
- A similar control stategy would be difficult to implement in the case where the coupling acts also on the x_2-coordinate, that is $L_2 \neq 0$, with a strong coupling strength, because of a more complex dynamical behaviour of the uncontrolled system in this case. In particular, the propositions 5.6 and 5.7 are no more true in this case because we have to take into account the coupling on the x_2-coordinates.
- By a continuity argument w.r.t. α, up to increasing the time T of the first step of the control algorithm, the proposed control strategy is robust w.r.t. variations of the homogeneous coupling strength $\alpha > 0$, provided that α belongs to a compact interval $[\alpha_0,\alpha_1]$ with $\alpha_0 \geq \alpha_s$.

C. Simulations

Assume $N = 4$ and $\theta_1 = 0.4$, $(\gamma_1,\gamma_2) = (0.2,0.8)$, $(k_1,k_2) = (0.5,1.4)$, $(\theta_1,\theta_2) = (0.4,1.2)$. This implies that $C_{\text{sync}} = 0$. On Figure 8(a), we have plotted the trajectories for the uncontrolled system for some arbitrary initial conditions and $\alpha \geq \alpha_s$: they converge to Φ_{01}. On Figure 8(b), we have plotted the trajectories for the controlled system with $\#S = 1 > C_{\text{sync}}$, in which only subsystem 2 is controlled, as in Section V-B.1, for some arbitrary initial conditions and $u_{\min} < \frac{\theta_2\gamma_2}{k_2}$: they converge to Φ_{10}.



(a) Convergence towards Φ_{01} for the uncontrolled system



(b) Convergence towards Φ_{10} with one controlled subsystem

Fig. 8. Control strategy in the strong coupling regime

In this case, the control towards Φ_{01} requires $\#S \geq N - C_{\text{sync}} = 4$, that is, every subsystem has to be controlled, and one can check that the proposed control strategy fails for $\#S < 4$. On every figure, subsystem 1 is in red, subsystem 2 is in green, subsystem 3 is in purple and subsystem 4 is in blue, that is, we have plotted the trajectories $(x_{1,k}(t), x_{2,k}(t))$ in these different colors for $k \in \{1, \dots, 4\}$. For these simulations we have chosen a coupling graph that is a chain. However, as already mentioned, the dynamical behaviour in the strong coupling regime does not depend on the topology of the coupling graph.

VI. Conclusion

The coupling of several similar systems through a diffusion mechanism leads to new dynamical behaviour for the coupled network: in the case of a network of bistable switches, new patterns of steady states are generated, depending on the number of systems in the network and the topology of the connection. These results are relevant to guarantee a desired outcome within a group of cells (pattern formation, tissue homeostasis) where the synchronization of similar gene regulatory networks is at play. We proposed a qualitative control strategy that allows to reach an arbitrary synchronization pattern in the weak regime. In the strong coupling regime most of these patterns are unstable, excepted full synchronized patterns, so that we proposed a control strategy in order to reach these states. A key feature of this strong coupling control strategy is that the variations of the control terms propagate through the network, so that it is sufficient to control a subset of the subsystems in order to control the whole system. These results open a new direction in the application of qualitative strategies to the synchronization of coupled identical systems. In future works, it would be interesting to extend our work to systems with an oscillatory individual dynamics, such as negative feedback loops, or to systems having more general coupling terms such as strongly heterogenous coupling strengths or non linear couplings.

Appendix: Stabilization of the individual system at its steady states

A. Controlled equation: single input acting on the two variables: symmetric stabilization strategy

Here we recall some facts taken from [6, Section 5]. Consider the controlled equation:

$$\begin{aligned} \dot{x}_1 &= -\gamma_1 x_1 + u k_1 s^-(x_2, \theta_2) \\ \dot{x}_2 &= -\gamma_2 x_2 + u k_2 s^-(x_1, \theta_1). \end{aligned} \tag{20}$$

The control $u \equiv u(t, x(t))$ is assumed to act on the production rates of each variable. It is assumed to depend only on $t \geq 0$ and on the domain $(B_{jk})_{j,k \in \{0,1\}}$ to which the solution $x(t)$ of Equation (20) at time t belongs, and u has values in a finite set of the form $\{u_{\min}, 1, u_{\max}\}$, where $u_{\max} \geq 1$ and $u_{\min} \geq 0$. Note that u changes the location of the focal points ϕ_{ij}. We make the following assumptions on the parameters of the system (for more details, see [6]):

$$\begin{aligned} &\theta_j < \frac{k_j}{\gamma_j}, \; j \in \{1,2\}; \\ &\frac{\theta_2}{\theta_1} > \frac{k_2}{k_1}\frac{\gamma_1}{\gamma_2}; \\ &\frac{\theta_2}{\theta_1} < \frac{k_2}{k_1}. \end{aligned} \tag{H}$$

1) Separatrix: The separatrix (S_u), which separates B_{00} into two regions $(S_u)^-$ and $(S_u)^+$ is defined, in the coordinates $(x_1, x_2) \in B_{00}$, for $u \geq 0$, as the curve of equation

$$x_2 = \alpha(x_1, u) = \frac{k_2 u}{\gamma_2} - \left(\frac{k_2 u}{\gamma_2} - \theta_2\right)\left(\frac{\frac{k_1 u}{\gamma_1} - x_1}{\frac{k_1 u}{\gamma_1} - \theta_1}\right)^{\frac{\gamma_2}{\gamma_1}}.$$

The curve (S_u) passes through (θ_1, θ_2) and divides K in two regions (above and below) such that the solutions of Equation (20) reach B_{01} or B_{10}, respectively, in finite time. Moreover, B_{10} (respectively, B_{10}) is included in the bassin of attraction of ϕ_{10} (respectively, ϕ_{01}). One can show that, under Assumption (H), one can choose $u^{01}_{\min}, u^{10}_{\min} < \min_{j \in \{1,2\}}\{\frac{\theta_j \gamma_j}{k_j}\}$, and $u_{\max} \geq 1$ such that $\frac{u^{01}_{\min} k_2}{\gamma_2} > \alpha(u^{01}_{\min}\frac{k_1}{\gamma_1}, u_{\max})$ (that is, $\left(\frac{u^{01}_{\min} k_1}{\gamma_1}, \frac{u^{01}_{\min} k_2}{\gamma_2}\right) \in (S_{u_{\max}})^+$) and $\frac{u^{10}_{\min} k_2}{\gamma_2} < \alpha(u^{10}_{\min}\frac{k_1}{\gamma_1}, u_{\max})$
(that is, $\left(\frac{u^{10}_{\min} k_1}{\gamma_1}, \frac{u^{10}_{\min} k_2}{\gamma_2}\right) \in (S_{u_{\max}})^-$).

2) Control algorithm: Here we present a control strategy, proposed in [6, Section 5].

- First phase: Choose $u \equiv u^{01}_{\min}$ (respectively, $u^{10}_{\min}$) during a time $T > 0$ large enough.
- Second phase: Choose $u \equiv u_{\max}$ until $x(t)$ enters in B_{01} (respectively, B_{10}).
- Third phase: Choose $u \equiv 1$ after $x(t)$ has entered in B_{01}.

During the first phase, every focal point of the system belongs to B_{00}, hence the solution $x(t)$ of Equation (20) converges towards the point $(u_{\min}\frac{k_1}{\gamma_1}, u_{\min}\frac{k_2}{\gamma_2}) \in B_{00}$ when $t \to \infty$. During the second phase, $x(t)$ reaches B_{01} or B_{10} in finite time, depending on the choice of $u \equiv u^{01}_{\min}$ or $u \equiv u^{10}_{\min}$. During the third phase, $x(t)$ converges towards ϕ_{01} or ϕ_{10}.

B. Controlled equation: single input acting on one variable: asymmetric stabilization strategy

Consider the controlled equation:

$$\begin{aligned} \dot{x}_1 &= -\gamma_1 x_1 + u k_1 s^-(x_2, \theta_2) \\ \dot{x}_2 &= -\gamma_2 x_2 + k_2 s^-(x_1, \theta_1), \end{aligned} \tag{21}$$

and assume that the condition $\theta_j < \frac{k_j}{\gamma_j},\ j \in \{1,2\}$ holds. Notice that, in this case, the assumptions made on the constants of the system are weaker than Condition (H). One can implement a strategy that stabilizes ϕ_{01}. In this case, global stabilization of ϕ_{10} is impossible because the equation is uncontrolled in the regular domain B_{01}. For this, we need to act on x_2.

1) Control algorithm: Here we present a stabilization strategy at ϕ_{01} for Equation (21). It is a simpler strategy than the symmetric one presented in Appendix VI-A.

- First phase: Choose $u \equiv u_{\min} < \frac{\gamma_1 \theta_1}{k_1}$. The focal points of Equation (21) all belong to $B_{00} \cup B_{01}$, and the focal point corresponding to the regular domain B_{00} belongs to B_{01}. Hence, $x(t)$ reaches B_{01} in finite time.
- Second phase: Choose $u \equiv 1$ after $x(t)$ has entered in B_{01}.

A similar strategy is valid for ϕ_{10}, assuming that the control acts on the production rate of x_2, replacing the condition $u_{\min} < \frac{\gamma_1 \theta_1}{k_1}$ by $u_{\min} < \frac{\gamma_2 \theta_2}{k_2}$.

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